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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,559	12/08/2004	Kenneth L. Arrington	21114YP	9984
210 7590 10/05/2007 MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907			EXAMINER LOEWE, SUN JAE Y	
			ART UNIT 1626	PAPER NUMBER
			MAIL DATE 10/05/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/517,559

Applicant(s)

ARRINGTON ET AL.

Examiner

Sun, Jae Y. Loewe

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 11-15 is/are allowed.
- 6) ☒ Claim(s) 1-8, 10 and 16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/27/2005.

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 and 10-16 are pending in the instant application. Claims 11-15 are allowed.
Claims 1-8, 10 and 16 are rejected.

Amendments & Arguments

2. Applicant's arguments and amendment submitted on July 26, 2007 were fully considered.

The following grounds of rejection/objection are withdrawn:

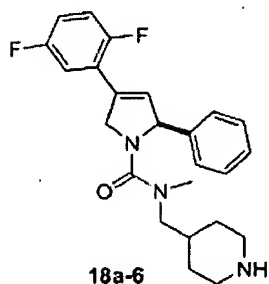
- a. The objection to the specification is withdrawn.
- b. The 35 USC 112 2nd paragraph rejection is withdrawn.

The following grounds of rejection/objection are maintained:

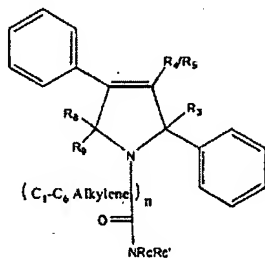
- c. Claims 1-8, 10 and 16 contain non-elected subject matter. This ground of objection is maintained (see below section 3).
- d. Applicant's arguments in response to the 35 USC 112 1st paragraph written description rejection of claims 1-8, 10 and 16 are not found fully persuasive. The scope of the disclosure was modified in view of Applicant's arguments.
However, for the reasons described in section 5 (below), this ground of rejection is maintained.
- e. Applicant's arguments in response to the 35 USC 112 1st paragraph enablement rejection of claims 1-8, 10 and 16 are not found persuasive. This ground of rejection is maintained.
- f. The provisional double patenting rejections are maintained (section 7).

Elected and Examined Subject Matter

3. An election of species was made on June 4, 2007 within the elected Group I, drawn to products. Applicant elected compound of example 18a-6.



The following subgenus, wherein $R_2=R_6=\text{phenyl}$, that includes the elected compound was searched and examined:



The full scope of this subgenus was not in compliance with the requirements of 35 USC § 112 1st paragraph (written description and enablement). Pursuant to MPEP 1893.03(d), subject matter outside of this subgenus but within the scope of Group I was not rejoined. It is asserted that the subject matter not rejoined is patentably distinct and non-elected.

The objection to claims 1-4, 6 and 7 for containing non-elected subject matter is maintained because the claims are drawn to $R_2/R_6=\text{aryl}$.

Information Disclosure Statement

4. The references of Iwasawa et al. and Ranjon et al. (IDS dated July 27, 2005) were considered. A signed copy of form 1449 is submitted herewith.

Claim Rejections – 35 USC § 112 – Written Description

5. The rejection with respect to variables R₃, R₄, R₈ and R₉ is withdrawn in view of Applicants amendment to the claims.

The rejection with respect to variables R₁₀, R_c and R_c' is maintained. The grounds of traversal in the response dated July 26, 2007 are addressed below.

- a. Applicants stated:

The Examiner states that Applicants merely reduced to practice four examples of a R¹⁰ substitution, namely a halogen, alkyl, cyano, and hydroxy group. However, Applicants respectfully maintain that the examples section of the specification illustrates at least eleven embodiments of R¹⁰ substitutions. Representative examples are illustrated below:

It is noted that the previous office action (page 7) stated:

Scope of Disclosure

Reduction to Practice: compounds representing the following substituents ...

R ₁₀	halogen, alkyl (opt subs halogen) CN, OH
R _c and R _c '	alkyl optionally substituted with the following <ul style="list-style-type: none">• OH, -CO₂H, alkoxy• (C=O)morpholine (optionally substituted alkyl)• O(C=O)-piperazine or piperidine or morpholine• phenyl, pyridine• oxazole, pyrazole, oxadiazole, thiazole, triazole• oxopyridine, oxotriazole• piperidine, piperazine• tetrahydrofuran, dioxolane, dioxane

Thus, R_c and R_c' were noted to represent alkyl optionally substituted with several embodiments of R₁₀. It is shown below that the originally stated scope of the

disclosure (above) encompasses eight of the eleven embodiments presented by Applicants as examples used to rebut the rejection (see section b and c).

- | | |
|----------------------|--|
| Rebuttal: | 1. (C=O) _a O _b C ₁ -C ₁₀ alkyl: |
| Scope Disclosure: | Methyl substituted on R ⁶ and Methyl substituted on R ² ;
R ₁₀ halogen, alkyl (opt subs halogen) |
| Rebuttal: | 2. (C=O) _a O _b aryl: Phenyl substituted on R ^C /R ^C |
| Scope Disclosure: | alkyl optionally substituted with the following ...
• phenyl, pyridine |
| Rebuttal: | 4. (C=O) _a O _b heterocyclyl: .. dioxolanyl, substituted on R ^C /R ^C |
| Scope of Disclosure: | alkyl optionally substituted with the following ...
• tetrahydrofuran, dioxolane, dioxane |
| Rebuttal: | 5. CO ₂ H: carbonyl substituted on R ^C /R ^C |
| Scope of Disclosure: | alkyl optionally substituted with the following ...
• OH, -CO ₂ H, alkoxy |
| Rebuttal: | 6. Halogen: F and Cl substituted on R ⁶ |
| Scope of Disclosure: | R ₁₀ halogen, |
| Rebuttal: | 7. CN: CN substituted on R ⁶ |
| Scope of Disclosure: | R ₁₀ ... CN, |
| Rebuttal: | 8. OH: substituted on R ^C /R ^C and OH substituted on R ² ; |
| Scope of Disclosure: | R ₁₀ ... OH
alkyl optionally substituted with the following
• OH, -CO ₂ H, alkoxy |
| Rebuttal: | 9. O _b C ₁ -C ₆ perfluoroalkyl: CF ₃ on R ⁶ |
| Scope of Disclosure: | R ₁₀ halogen, alkyl (opt subs halogen) |

- b. In view of Applicants arguments, the scope of the disclosure is broadened to encompass the following embodiments of R₁₀ (for substitution on R_c and R_c' only):

C₂-C₁₀ alkenyl,
C₂-C₁₀ alkynyl,
alkyl optionally substituted with pyrrolidinyl
Amino groups substituted on R^C/R^{C'}
Sulfonyl group substituted on R^C/R^{C'}

c. Conclusions from Sections b and c:

- i. The support for variable R₁₀ in the disclosure differs depending on whether it is a substituent to R₂/R₆ or to R_C/R_{C'}.
- ii. The disclosure supports R₁₀= halogen, alkyl (opt subs halogen) CN, OH for substitution on R₂/R₆. Applicant's rebuttal provides evidence for this same conclusion.
- iii. The disclosure supports R₁₀ encompassed by the following, when R₁₀ is a substituent on R_C/R_{C'}:

alkyl optionally substituted with the following

- OH, -CO₂H, alkoxy
- (C=O)morpholine (optionally substituted alkyl)
- O(C=O)-piperazine or piperidine or morpholine
- phenyl, pyridine
- oxazole, pyrazole, oxadiazole, thiazole, triazole
- oxopyridine, oxotriazole
- piperidine, piperazine
- tetrahydrofuran, dioxolane, dioxane

pyrrolidinyl

and

C₂-C₁₀ alkenyl,
C₂-C₁₀ alkynyl,
Amino groups substituted on R^C/R^{C'}
Sulfonyl group substituted on R^C/R^{C'}

- d. In view of Applicant's arguments the support for R_C and R_{C'} is broadened to encompass all of the following:

R_c and R_c' together form morpholine, azetidine, pyrrolidine
hydrogen
morpholine, piperazine, pyrrolidine, piperidine
cycloalkyl

- phenyl, pyridine
- oxazole, pyrazole, oxadiazole, thiazole, triazole
- oxopyridine, oxotriazole
- piperidine, piperazine
- tetrahydrofuran, dioxolane, dioxane

- e. Even in view of the current modification of the scope of disclosure (above sections a-d), it is maintained that variables R_{10} , R_c and R_c' are still claimed broader than what is supported by the specification. For example:

R^{10} = halogen, alkyl (opt subs halogen), CN, OH – ie. substituents to R^2 and R^6 – does not provide sufficient support for the broad range claimed for R^{10} =

1) $(C=O)_aO_bC_1-C_{10}$ alkyl, wherein a and b are not zero 2) $(C=O)_aO_b$ aryl, for any value of a and b, etc;

R_c and R_c' together forming morpholine, azetidine, pyrrolidine does not provide sufficient support for the genus of

R_c and R_c' can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said

Claim Rejections – 35 USC § 112 – Enablement

6. Applicant's arguments with respect to enablement for making the scope of compounds generically claimed is not herein addressed for the following reason. The claims were not rejected for lack of enablement for making the compounds, rather, the claims rejected for lack of

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enablement for using the compounds that are unsupported by the disclosure. One argument that can be applied as rebuttal for the enablement rejection is addressed below.

Applicant argues:

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 195 USPQ 150, 153 (1977): "[A] considerable amount of experimentation is permissible...if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re*

This argument is not found persuasive for the following reason. In view of the level of unpredictability in the art of inhibiting KSP, one of ordinary skill would not be enabled to determine which (if any) of the structural parameters not tested/exemplified, would lead to compounds that are active. The specification does not provide any support for why the numerous variables claimed (that are not represented), are structurally tolerated for activity. Specifically, the only structural motif that is preserved in all compounds generically claimed is a 2,5-dihydropyrrole core. In view of the large variability in structure (for example, R2/R6 can be substituted with heterocycle which can be further substituted with heterocycle), which lead to compounds that are significantly different from those reduced to practice, for enablement of using the full scope of the compounds claimed, it may be assumed that the presence 2,5-dihydropyrrole core is the only structural feature required for KSP inhibiting activity. If this is the case, Applicant is invited to clarify this on the record. Absent clarification or further guidance, it is maintained that the specification does not support enablement for using the full scope of compounds generically claimed.

The 353 USC 112 1st paragraph enablement rejection is maintained.

Double Patenting

7. MPEP 804.I.B. states:

The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.

In view of the grounds of rejections maintained as detailed in sections 3-6 (above), this ground of rejection is also maintained.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

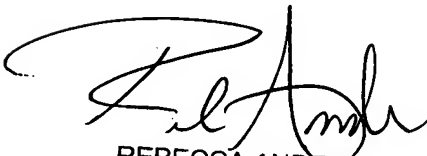
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe
Art Unit 1626



REBECCA ANDERSON
PRIMARY EXAMINER